DEVELOPMENT OF MUCOADHESIVE SUSTAINED RELEASE TABLET OF CURCUMIN FOR GASTRIC WOUND HEALING MANAGEMENT

A Synopsis

Submitted in

Partial fulfillment for the degree

Of

Doctor of Philosophy
(Pharmacy)

Supervised By:
JV'n Dr. (Prof.) Dharmendra Ahuja

Submitted By:
JV'n Preeti Singh

Enroll. No.: JVR- II/17/10086

Faculty of Pharmaceutical Sciences
Jayoti Vidyapeeth Women's University, Jaipur (Rajasthan)

July, 2018

INTRODUCTION

Drug events can be enhanced by new drug delivery system, such as mucoadhesive system. These system relics in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to improvement in both local and systemic effects. Mucoadhesion is a topic of current significance in the design of drug delivery systems. Mucoadhesive drug delivery system extend the dwelling time of the dosage form at the site of absorption and make easy an intimate contact of the dosage form with the emphasize absorption surface and thus contribute to enhanced and / or better restorative presentation of the drug. The progression of mucoadhesion concerning a polymeric drug delivery display place is a complex one that includes wetting, adsorption and interpenetration of polymer chains along with a mixture of other processes. There are various factor influences the Gastro-Intestinal preservation and mucoadhesion (Dodou D et al, 2005).

This delivery system describes some exertion to enlarge the dwelling time of drug dosage forms in GI tract, by gastro retentive units and bioadhesive gastrointestinal patches. Numerous gastrointestinal patch systems provide bioadhesion, drug safety and unidirectional liberate, (Kinloch AJ, 1989). This recipe of function could advance the overall oral bioavailability. Dosage forms planned for mucoadhesive drug delivery should be small and elastic enough to be satisfactory for patients and should not cause impatience. Other most wanted characteristics of a mucoadhesive dosage form include high drug loading capacity, controlled drug release (rather unidirectional release), good quality mucoadhesive properties, smooth surface, tastelessness, and well-situated application (Jiménez-Castellanos MR et al, 1993). Erodible formulations can be beneficial because they do not require system reclamation at the end of desired dosing period. A number of appropriate mucoadhesive dosage forms have been residential for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been deliver via the mucosal route, even though with moderately low bioavailability (0.1–5%),owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa (Shinde AJ, 2008).

There are lots of routes of mucoadhesive drug delivery system, oral route is the the majority antique as well as chosen by patient being suitable to take. However peroral route has

shortcomings such as hepatic first pass metabolism and enzymatic squalor in GIT which is a impediment to the absorption of most proteins and peptides groups of drugs (Flávia Chiva Carvalho at el, 2010). Mucoadhesion can be achieve by using mucoadhesive polymers. There are different types of mucoadhesive polymers are presented. covered devices have been developed to achieve constant drug release (Ahuja A et al, 1997). Mucoadhesive drug delivery systems are delivery systems which exploit the belongings of bioadhesion of confident polymers which become adhesive on hydration and hence can be used for targeting a drug to a exacting region of the body for absolute periods of time (Rakesh das, 2011). This is because the intestinal mucosa has a spread of even muscle and reasonably stationary mucosa, which makes it a more advantageous region for retentive systems. Thus, the intestinal mucosa is more suitable for persistent direction of drug delivery (Mishra S et al, 2012).

Persistent Release Drug Delivery System (SRDDS) is intended to release a drug at a preprogrammed rate by maintaining a stable drug level for a precise period of time with lowest amount side effects (Rohini D et al, 2012). Now a day's focus on the progress of SRDDS has increased, as very few drugs are coming out of do research and expansion and already obtainable drugs are affliction the problem of struggle due to their unfounded use particularly in case of drugs like antibiotics (Sahilhusen I Jethara et al, 2014). The most important goal of scheming SR formulations was intended to modify and improve the drug presentation by growing the duration of drug action, decrease the dosing regularity, condensed side effects, declining the required dose engaged and provided that the shortest possible time by using smallest amount of drug administered by the most appropriate route (Davis SS et al, 1984).

Jain S et al (2011) SR dosage forms are intended to convey the blood stage of a drug directly to therapeutic concentrations by earnings of an original dose portion and then sustain this level for convinced predetermined time with the maintenance portion. SR of drugs in GI tract following oral management is not affected by the absorption process. The major goal of SR dosage forms is the development of drug therapy assessed by the association between advantages and disadvantages of the use of SR systems**.** Davis R.D 2011 The present evaluation article is useful in acquaintance of tinted formulation approaches, criteria for drug selection, different countries sustained release dosage form patents and advance novel research for SRDDS. Shridhar GS, et al 2013.The present review is concerned with the patent study of drug release

through controlled or sustained release dosage forms. This patent review is useful in knowledge of sustained release dosage forms for its application.

Ideal chattels of delivery system

It should be efficiently immersed by oral route and steady in gastro-intestinal (GI) fluid.

Drugs that have small half-lives (2-4 hrs) are ideal drug applicant for formulation into SR dosage forms eg. Captopril, Salbutamol sulphate.

The dose of drug should not be less than 0.5gm and greatest dose of drug for scheming SRDDS is 1.0 gm eg. Metronidazole.

The therapeutic variety of the drug should be elevated in SRDDS for drug should have large beneficial range enough such that deviation in the liberate does not result in attention away from the lowest amount toxic levels.

Advantages of oral mucoadhesive drug delivery systems:

Prolongs the dwelling time of the dosage form at the site of incorporation, hence increases the bioavailability.

Excellent accessibility, rapid onset of action.

Drug is confined from poverty in the acidic surroundings in the git.

Improved patient compliance.

The incidence of drug organization is reduced.

Patient observance can be superior.

Drug administration can be completing more suitable as well.

The blood level fluctuation attribute of multiple dosing of predictable dosage forms is reduced.

improved manage of drug absorption can be attain, since the high blood level peaks that may be pragmatic after direction of a dose of a high ease of use drug can be compact.

Disadvantages of mucoadhesive drug delivery systems:

One of the most important borders in the growth of oral mucosal delivery is the be short of a good replica for in vitro broadcast to make out drugs appropriate for such administration.

Patient acceptability in terms to taste and irritancy.

consumption and Drinking is forbidden.

Smart JD et al (2005) The arrangement of non-covalent bonds such as hydrogen bonds and ionic interactions or physical entanglements flanked by the mucus gel layer and polymers provide a good mucoadhesion. Chickering DE et al 1999 The habitation time of dosage forms on the GI-mucosa should be extended, which allows a constant drug release at a given target site to exploit the salutary effect which is mediated by mucoadhesive polymers. For the purpose of local therapy or of drug discharge at the 'absorption window' mucoadhesive drug delivery systems can be restricted on a certain surface area instead of the GI-segment, where drug absorption takes place. Dodou D et al 2005 Mucoadhesive polymers like poly (acrylates) such as carbomers are supposed to bind via hydrogen bonds, while chitosans seem to bind via ionic communications between their primary amino substructures and sialic acid and sulfonic acid substructures of the mucus. Mucoadhesive polymers considerably prolong the dwelling time of dosage forms on the mucosa and hence the nonstop drug release at a given target site.

In natural systems, four types of bio-adhesion could be distinguished:

• Adhesion of a standard cell on another standard cell

• Adhesion of a cell with a strange substance

• Adhesion of a usual cell to a pathological cell

• sticking together of an adhesive to a biological substance For drug delivery purpose, the term bio-adhesion imply addition of a drug delivery service system to a specific biological location.

Pharmaceutical deliberation and formulation plan for successful gastro-intestinal mucosal drug delivery system

Drug choice for gastrointestinal mucosal delivery is partial by the physicochemical properties of the drugs themselves. To be delivered trans-mucosally, drugs must have exclusive physicochemical properties, i.e. a correct balance flanked by solubility and lipophilicity. Currently, new program of drugs are naturally not residential exclusively for oral trans-mucosal delivery. It is also significant to believe factors influencing drug release from a scheme. The release kinetics of a specified drug from a system could be governed principally by the polymer morphology and excipients existing in the system. Finally, perfect formulation and its deprivation products should be non-toxic, non irritation and free from leachable impurities. It should not aid in enlargement of secondary infections and avoid the effects of local drug impatience at the site of function. An ideal gastrointestinal mucosal drug delivery system must meet several fundamentals to be successful. The first precondition for a gastrointestinal mucosal drug delivery system is that it should rapidly attach to the mucosal surface and sustain strong dealings to prevent displacement. Impulsive adhesion of the system at the target site is serious and can be achieve throughout mucoadhesive polymers. Make contact with time should also be adequately long at the target site, usually longer than that desirable for absolute drug release. The second requirement for a unbeaten and effective gastrointestinal mucosal drug delivery system is that the bio-adhesion presentation should not be impacted by adjoining environmental pH.

Other advantageous uniqueness of a gastrointestinal mucosal drug delivery system includes towering drug loading, absolute drug release, and suitable direction. Drug release from a polymeric substance takes place either by the dispersion or by polymer deprivation or by their mixture. Polymer dilapidation usually takes place by the enzymes or hydrolysis. This may occur in the form of bulk erosion or exterior erosion. It is also significant to believe factors influencing drug release from a polymer. The release kinetics of a given drug from a polymeric medium could be governed principally by the polymer morphology and excipients present in the system.

REVIEW OF LITERATURE

Schnürch AB (2005) In the current years, mucoadhesion drug delivery system has exposed amazing interest for growing the residence time at the site where it is useful and to accelerate close contact of the dosage form with the essential mucosa, mostly to encourage absorption and raise the proportion bioavailability of drug due to its broad surface area and elevated flow rate of blood. Mucosal drug delivery bypass the hepatic first-pass thus avoids the deprivation depravity by enzymes present in gastrointestinal tract.

Khan Ab et al, (2014) this system could be assess in delivering an enlarging number of high molecular weight molecules like proteins and peptides. Mucoadhesive restricted drug delivery systems are precious, since they not only give a prohibited but also targeted release and thus site specific delivery.

Bhatt DA et al, (2011) gastrointestinal mucosa is also an essential site for the advancement of mucoadhesive dosage forms for growing GI transit time as well as bioavailability. The possible amount of local ulcers as a side effect due to the close contact of the dosage form with GIT mucosa for absolute periods of time should not be deserted **(Shaikh TR et al, 2011).**

Khurana SH et al (2011), the mucus earnings, that is the interminable production of mucous by the gastric mucosa to reinstate the lost mucous through peristaltic contractions and the intensity of the stomach contented also limits the potential of mucoadhesion as a gastro retentive force.

Shaikh R et al (2011) The perception of mucoadhesion has provided the immense purpose in prolonging the dwelling time as well as controlled release outcome of a variety of bioadhesive dosage forms through different mucosal routes. The formulations based on the mucoadhesive drug delivery system have shown the improved bioavailability of several drugs. The use of different mucoadhesive polymers have achieved the important attention in formulating the sustained release, comprehensive release as well as extended release dosage forms.

Kumar K et al (2014) the mucoadhesive drug delivery provides better absorption and improved bioavailability of dosage forms due to the bulky surface area and superior blood flow in the mucosal cavities. The release across the mucus membrane provides a range of compensation over other drug delivery routes i.e., surmount the hepatic first pass metabolism as well as the degradation of drugs by different gastrointestinal enzymes as well as intestinal flora .

Lalla JK et al (2002) for the preferred mucoadhesive potency of the mucoadhesive dosage forms, there are various mucoadhesive polymers that can be used. These polymers are moreover usual or synthetic macromolecules which are able of adhering to the mucosal surfaces.

Alexander A et al (2011) From last three decades, the use of different mucoadhesive polymers has achieved a immense interest in the field of pharmaceutical technology. these days, the use of mucoadhesive polymers has been acknowledged as an central strategy to prolong the residence time and to get better the contained effects of drug delivery systems on various mucus membranes of a biological system.

Ramana et al (2007), by intended and evaluated the buccal mucoadhesive drug delivery systems of Metoprolol Tartrate using the mucoadhesive polymers i.e., Carbopol-934, hydroxy methyl propyl cellulose, hydroxyl ethyl cellulose and sodium carboxy methyl cellulose. The greatest mucoadhesive performance and *in-vitro* drug release outline were exhibited by tablets containing hydroxyethyl cellulose and Carbopol-934.

Kolli et al (2008) residential the buccal mucoadhesive patch of Prochlorperazine by means of different concentration of HPMC E15 and Polyester assistance membrane. They accomplished that the formulation containing 2500 mg of HPMC E15 and 375 µl of Propylene glycol was the optimized formulation after evaluating it in-vitro as well as ex-vivo studies.

Naga Raju et al (2011) formulated the buccal tablets of Metoprolol Tartrate via different Mucoadhesive polymers such as Carbopol 934, Sodium alginate and HPMC K4M in grouping. The prepared tablets were evaluated for bioadhesive potency and *in-vitro* drug release. *In-vitro* bioadhesive strength and *in-vitro* release studies showed that formulation containing 1:1.25 relative amount of drug and polymer (Carbopol-934 and HPMC K4M) recipe showed optimum bioadhesive and exhibited most favorable drug release (77.33 ± 0.23) .

Mishra et al (2012) formulated the buccal patches of Simvastatin. The buccal patchs were arranged from 1% eudragit-RS100 and changeable quantity of dissimilar polymer compound, PVP, PVA, HPMC and EC. The formulation containing eudragit-RS100 and PVP(1:1) showed the greatest and quicker release .

Sandhya et al (**2013)** formulated buccal films of Ketorolac Tromethamine. These films were arranged by polymers like HPMC K 100M, HPMC E15, HPMC E50, Eudragit RLPO and residential by solvent casting method. Formulation F5 (HPMC E15-Polysorbate - Eudragit RLPO) exhibited best mucoadhesive presentation and matrix controlled release. enlargement behaviour and extent of mucoadhesion are significant factors in the selection of suitable formulation.

Velmurugan S et al (2013) was conducted a revise on Formulation and *in-vitro* evaluation of Losartan Potassium mucoadhesive buccal tablets by Velmurugan et al. They used mucoadhesive polymers such as Carbopol -940P, pectin, sodium CMC, Sodium alginate, HPMC K4M, HPMC K15M and HPMC K100M in unaccompanied and in grouping as release retarding agent to extend the drug release and to avoid first pass metabolism. *Ex-vivo* mucoadhesive potency, *ex vivo* dwelling time and in-vitro discharge studies showed that formulation F10 (sodium alginate and HPMC K100M) containing 1:1.25 ratio of drug and polymer combination showed reasonable bioadhesive and exhibited most advantageous drug release (91.33 % after 12 hrs) .

Ganaie et al, (2014) formulated the mucoadhesive buccal film of Methyldopa by means of using Hydroxy propyl methyl cellulose K-47 (HPMC K-47), poly vinyl pyrrolidine K-30 (PVP K-30), sodium CMC and ethyl cellulose. The most excellent mucoadhesive presentation and matrix controlled release was exhibited by the formulation F5 (HPMC K-47 and PVP K-30). The association correlation coefficient value (r) indicates the kinetic of drug liberate relaeasing pattern was zero order .

Madhuri et al, (2015) considered the solid dosage form for buccal drug delivery of Diltiazem Hydrochloride using a variety of polymers i.e., Carbopol971P (CP) and consequential

polymers such as Hydroxy propyl methyl bran (HPMCK4M) and Psyllium shell in seven formulations. They accomplished that the formulation B3 containing Carbopol971P and HPMC K4M in the percentage of 1:5 showed good quality mucoadhesive potency (51.34 gm) and greatest drug release of 94.72% in 8 hrs. enlargement of tablets increased with increase in deliberation of HPMC K4M.

Nagarani et al, (2016) formulated the Esomeprazole mucoadhesive buccal tablets by means of mucoadhesive polymers like hydroxy propyl methyl cellulose K 100 M, Carbopol 934, HPMC K 15 M. Drug: polymer proportion for F5 is 1:1, this F5 (guar gum and carbopol - 971P) formulation was measured as an optimized formulation surrounded by all these formulations for the reason that it released greatest quantity of drug in preferred period of 6 hrs and showed good enlargement index properties.

In 2016, the additional study was conducted by **Marimutho et al.** On formulation and assessment of Zidovudine mucoadhesive buccal patches using polymers i.e., HPMC E15, Sodium Alginate and gelatine. They accomplished that the release of Zidovudine from the formulated patches followed zero order kinetics so that the drug liberate mechanism was restricted release.

De R et al, (2009) Curcuma longa L. (Zingiberaceae family) and its polyphenolic compound curcumin have been subjected to a multiplicity of antimicrobial investigations due to widespread traditional uses and short side effects. Antimicrobial behavior for curcumin and rhizome extort of C. longa alongside different bacteria, viruses, fungi, and parasites have been reported. The capable results for antimicrobial activity of curcumin made it a superior applicant to develop the inhibitory consequence of existing antimicrobial agents through synergism. Indeed, dissimilar investigations have been done to enhance the antimicrobial activity of curcumin, together with synthesis of different substance derivatives to enlarge its water solubility as well as cell up take of curcumin. To be summarize previous antimicrobial studies of curcumin towards its application in the prospect studies as a natural antimicrobial agent..

Rambir Singh et al, (2002) Curcuma longa rhizome has been conventionally used as antimicrobial agent as well as an creature repellant. numerous studies have reported the universal antimicrobial activity for curcumin together with antibacterial, antiviral, antifungal, and antimalarial activities.

Wang Y J et al, (1997) The explosion of drug challenging microbial strains necessitate the studies for synergistic special effects of antibiotics in grouping with plant's derivatives to expand the antimicrobial combination with a wider range of activity and decline of adverse side effects of antimicrobial agents. Staph. aureus resistance to the penicillin group of antibiotics is growing connected with outward show of adverse side effects such as hypersensitivity and anaphylactic reactions.

Gowthamarajan K et al, were formulated mucoadhesive buccal tablets of curcumin using a expected mucodhesive polymer resultant from cashew nut tree gum (20% concentration), enhancer, 40mg assistance layer and (0.1% penetration). From the assessment studies, it was establish to be stable with a choice of physicochemical, in-vitro drug release and small term constancy 37 assessment and drug releases was followed anomalous diffusion. They were from the based their conclusions that cashew nut tree gum can be used as a mucoadhesive polymer to formulate buccal tablets with dormant mucoadhesive property.

Munasur A P et al. to study the attain of multipolymeric blends such as poly acrylic acid (PAA), poly vinyl pyrrolidone (PVP) and CMC on muco-adhesivity and controlled drug release for propranolol HCl matrices by employing Box-Behnken investigational plan. The most favorable buccal tablet formulation was probable for surface pH, hydration dynamics, release kinetics, mucoadhesiveness and distension/erosion. The consequence result explained with the intention of it would be prospective for buccal drug delivery system.

Gowthamarajan K et al. were formulated mucoadhesive buccal tablets of curcumin by means of using a natural mucodhesive polymer resultant from cashew nut tree gum (20% attention), enhancer, 40mg backing layer and (0.1% penetration). From the estimation studies, it was establish to be constant with a variety of physicochemical, in-vitro drug release and small term constancy 37 evaluation and drug releases was followed irregular diffusion. They were

from the based their results and findings that cashew nut tree gum can be used as a mucoadhesive polymer to formulate buccal tablets with dormant mucoadhesive property.

Senel S et al. were reported that formulation of bioadhesive buccal tablet arranged with different proportion of hydroxypropyl methylcellulose and carbomer using sodium glycodeoxycholate (GDC) as a incursion enhancer and outcome were exhibits good quality in vitro bioadhesion property lacking of affecting the histological changes such as loss of greater cell layers and the construction of vacuoles as well enlargement in the cells after 4 h contact by sodium glycodeoxycholate.

Soliman Mohammadi-Samani et al. were developed the technique for the research preparation of prednisolone buccoadhesive tablets by using polymers such as hydroxyl propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (NaCMC) and carbopol 934 (Cp 934). It was experiential from consequences results that the release rates of drug from formulation arranged with HPMC with viscosity grade 60 mPas and Cp 934 alone was quick and their mucoadhesion force was low as well. However, HPMC viscosity grade 500 mPas and NaCMC depicts moderate mucoadhesion.

Gavaskar B et al. has to developed mucoadhesive buccal multilayered tablets by using bioadhesive polymers like methocel K15M, Sodium methyl cellulose (NaMC), and sodium alginate. The results practical from the assessment of different parameters such as content equivalence, weight equivalence, breadth, surface pH, Swelling index, ex-vivo mucoadhesive strength, hardness, in-vitro drug permeation and in-vitro drug release. It accomplished and fulfillment in the current work that mucoadhesive buccal tablets of baclofen be able to extend the bio availability.

Akbari J et al Mucoadhesive tablets containing chlorehexidine were formulated by utilizing a combination of Chitosan and HPMC by employing straight compression method. The bioadhesive strength, in vitro drug release be carried out in organize to know the type of drug release and also the release facts were subjected to dissimilar release kinetic models for release mechanisms. The portion of HPMC in the mix together increased, the drug release rate compact with a lowest liberate rate and when HPMC was utilized unaccompanied as bioadhesive polymer were pragmatic from the outcome by Akbari J et. Al.

Ramana MV was formulated of metoprolol tartrate tablets by using carbopol-934; HPMC, HEC and CMC through direct compression. The formulations were differentiate for physiochemical factors, in-vitro release studies, in-vivo placebo studies and mucoadhesive presentation. The most outstanding mucoadhesive possessions and in-vitro drug release profile were discovered by the tablets containing Carbopol-934 and hydroxyethylcellulose in ratio 2:2.

Amit B et al, (2012) has organized and estimated mucoadhesive capsule enclose microspheres of drugs clarithromycin and omeprazole to take care of treat H. pylori infection. Drug entrapment effeciency, swelling and adhesion property and in-vitro drug release of microspheres were evaluate. The consequence result of the study showed that the capsule contain microspheres of drugs clarithromycin and omeprazole can be under attack to the stomach; hence drugs dwelling time at absorption site was improved. So drug residue at absorption site for expanded period of time which is most advantageous to treat H. Pylori infection.

Arya RKK et al, (2010) has arranged and characterize mucoadhesive microspheres of famotidine for continuation of gastric residence time. The w/o emulsification solvent disappearance/evaporation method was designed for the preparation of microspheres. Sodium Carboxy Methyl Cellulose (Sodium CMC) was used as a mucoadhesive polymers, and sodium alginate as a release scheming polymer. good quality muchoadhesion and superior entrapment efficiency was achieve by by means of hydrophilic polymer, Sodium CMC. The prepared microspheres exhibit extended drug release for 8h. As the attention of sodium alginate enlarged, the mean particle size also increased but rate of the drug release decreased. The mucoadhesion increased, as the sodium CMC polymer attention increase.

Patel JK et al, (2009) formulated and evaluated in-vitro and in-vivo performances mucoadhesive microspheres of amoxicillin for the probable use in the management of Helicobacter pylori. Carbopol-934P was used as mucoadhesive polymer and ethyl cellulose as carrier polymer for the groundwork of mucoadhesive microspheres. Broadcast screening of the emulsifying agent, time for magnificent, drug-to-polymers ratio and velocity of rotation was carried out. An in-vitro mucoadhesive test showed that microspheres adhered added strongly to the gastric mucous film layer for an extensive period of time. A sustained drug release was obtain for more than 12 h to 15 hrs. In- vitro release test showed that amoxicillin released faintly

faster in acidic medium than in alkaline medium. In-vivo H. pylori clearance tests were also approved out by administering amoxicillin powder and mucoadhesive microspheres to H. pylori infectious wistar rats. The consequences result showed that amoxicillin mucoadhesive microspheres had a enhanced clearance effect than amoxicillin powder.

Thong-Ngam D and Chatsuwan T, (2007) evaluate the in-vitro impending of preferred herbal plants, namely Aloe vera, curcumin, garlic, and plau-noi against H. pylori. A typical standard strain (NCTC 11637) and 9 scientific isolates of H. pylori were used to evaluate antibacterial movement of four herbal substances, employing an agar strength dilution and diskette diffusion method. The disk diffusion was experienced using varying amounts of herbal substance at 20, 50, 100, 200 and 400µg. The smallest amount inhibitory concentrations (MICs) of Aloe vera, curcumin, garlic, and plau-noi were >512, 64, >512, >512µg /mL, correspondingly respective. They conclude that curcumin exhibited probable of in-vitro antibacterial activity against H. pylori, which suggests that it may be helpful for the treatment of H. pylori infection. conversely, Aloe vera, garlic, and plau-noi did not demonstrate any antibacterial activity against H. pylori.

Ronita D et al, (2009) examine the in-vitro and in-vivo antibacterial potential of curcumin. The in-vitro antibacterial activity of curcumin was performed against 65 clinical isolates of Indian H. pylori strains. In-vivo, the antimicrobial effect of curcumin in H. pylori-infected C57BL/6 mice was examined. Apart from anti-H. pylroi actvitiy, its efficacy in reducing the gastric damage due to infection were also examined histologically. The MIC of curcumin against H. pylori growth was found to be in ranges from 5µg/ml to 50 µg/ml. This learning provides original insights into the therapeutic outcome of curcumin against H. pylori infection, suggesting its utility as an alternative therapy against H. pylori infection. Pant P et al., (2011) has formulated mucoadhesive microspheres of clarithromycin as a gastro retentive drug delivery system to intention the H. pyroli in ulcer patients. The microspheres were prepared using sodium alginate and hydroxypropyl methylcellulose (HPMC) as polymer by ionic gelation technique. HPMC used as a mucoadhesive polymer and sodium alginate used to control the release rate. The study revealed that both the polymers (HPMC and sodium alginate) used in the formulation of microspheres have a significant effect on the mucoadhesion, drug entrapment efficiency and in-vitro drug release. After evaluating all the formulations, the formulation which has the higher

percentage of HPMC showed good entrapment efficiency (63%), mucoadhesion about 79.6% as well as good release profile in 8 hrs.

Kundu P et al, (2011) have exposed that cur cumin is capable of eradicating H. pylori infection in mice. They examined the mechanism by which curcumin protects H. pylori infection in cultured cells and mice. They investigated the role of curcumin on inflammatory matrix metalloproteinases (MMPs) as well as proinflammatory molecules. Since, MMP-3 and MMP-9 are inflammatory molecules associated to the pathogenesis of H. pylori infection. Curcumin dose dependently suppressed MMP-3 and -9 expression in H. pylori infected human gastric epithelial (AGS) cells. Consistently, H. pylori eradication by curcumin-therapy involved significant downregulation of MMP-3 and -9 activities and expression in both cytotoxic associated gene (cag)+ve and cag-ve H. pylori infected mouse gastric tissues. Both curcumin and triple therapy were associated with MMP-3 and -9 downregulation during H. pylori eradication, but unlike triple therapy, curcumin enhanced peroxisome proliferator activated receptor-γ and inhibitor of kappa B-α. The result indicated that curcumin-mediated healing of H. pylori infection involves regulation of MMP-3 and -9 activities.

Yadav VK et al, (2011) considered the gastro retentive dosage forms of repaglinide as controlled-release drug delivery systems to enlarge its dwelling time in the stomach. The dosage form was achieved through the preparation of mucoadhesive microspheres by the emulsion solvent evaporation technique consisting of chitosan as a mucoadhesive polymer and Eudragit RS-100 as rate controlling polymer. The drug liberate was also establish to be slow and extended for 24 h. In-vivo testing of the mucoadhesive microspheres in diabetic albino rats verified important antidiabetic outcome of repaglinide. The hypoglycemic outcome obtained by mucoadhesive microspheres was intended for more than 16 h whereas repaglinide formed an antidiabetic outcome for only 10 h suggesting to facilitate mucoadhesive microspheres are a precious scheme for the long term delivery of repaglinide.

Sambathkumar R et al (2011), discussed concerning H. pylori infection and interrelated chronic active gastritis and duodenal ulcer (DU). Triple therapy (proton pump inhibitor [PPI], amoxicillin and clarithromycin), is most successful and universal treatment. These three drugs prescribed twice a day for 1 week. However, some clinical trials and reports indicate that combination therapies cannot bring out complete eradication of H. pylori. Probably short

residence time of anti-H. pylori agents in the stomach is one of the main reason for incomplete eradication. Due to short dwelling time the effective antimicrobial concentrations cannot be achieved in the gastric mucous layer or epithelial cell surfaces where H. pylori exists. To overcome this difficulty or to develop the efficacy in eradicating the infection is to transport the antibiotic locally in the stomach. Considering beyond issue, they prepared mucoadhesive microspheres of clarithromycin for the treatment of H.pylori infection. The microspheres have prepared by emulsification interior gelation technique, using sodium alginate alone and in combination with HPMC K4M and Carbopol 974 P. The maximum incorporation efficiency was found to be 93 %. Microspheres were spherical in shape examined by the scanning electron microscope. The in-vitro bioadhesion study indicated the good quality mucoadhesive properties of microspheres. Thus, gastroretentive drug delivery advance approach show great promise in the treatment of H. Pylori infection.

OBJECTIVES:

The aim of the work is to improve the bioavailability of curcumin by gastrointestinal tract and to study in-vitro and in-vivo drug release.

The main object to treat Gastric Wound Healing and Pain Management.

To improve and prolong the residence time of the dosage form at the site of absorption and facilitate an intimate contact of the dosage form.

To improve the therapeutic better effect of the drug.

To approach great promise in the treatment of H. Pylori and kill the microbes.

To prevent microbial infections.

MATERIALS AND METHOD

Extraction of Curcumin

The 250 gm rhizome of *Curcuma longa* was dried and powdered.Then it was allowed to stuff into the soxhlet apparatus andextraction wasinitiated with solvent 90% alcohol of about 250 ml,for about 72 hrs at 45- 50 º C. The extract was decolorized withactivated charcoal and then concentrate. Which was dried in roomtemperature overnight, yielding 6 gm of *curcumin.*

Preparation of mucoadhesives tablet :

Curcumin will use for extraction of mucoadhesive polymers were obtained from local market. All other synthetic chemicals used in formulation will obtaine from Merk..

Materials: Curcumin, Xanthan gum, Guar gum, HPMC E15, Permeation enhancer, FTIR, Direct compression, unidirectional flow.

The mucoadhesive tablets were formulated by direct compression method using hydrophilic polymers such as guar gum, xanthan gum, HPMC E15 in different concentration and piperine as permeation enhancers (1%). Ethylcellulose is used as backing layer to promote the unidirectional flow of drug in the intestine region region. Curcumin has a number of beneficial activities, such as potent antioxidant, anti-inflammatory, anticancer, anti-rheumatic and anti-diabetic. The FT-IR spectra of pure drug with different polymers showed no shift in peak, indicating absence of interaction. The prepared formulations were evaluated for pre-compression studies such as bulk density, tapped density, angle of repose. The post-compressions studies such as weight variation, thickness, friability, hardness, mucoadhesive strength, drug content, enlargement studies, in-vitro diffusion flow studies and in-vitro dissolution studies.

Preparation of mucoadhesive sustained release tablet of curcumin:

Curcumin mucoadhesive sustain release tablets were formulated wet granulation method. The formulation composition of different batch. All the powders passed all the way through 40 mesh sieve. The required quantity of Curcumin, various polymers and fillers will mix thoroughly. And prepare 10% polyvinyl-Pyrrolidone solution in isopropyl-alcohol for the wet mass prepared to granules pass through 18 mesh size sieve. Granules kept in Trayed Dryer for 1 hrs.after the drying of granules pass through 16 mesh size sieve. Magnesium stearate and talc were finally

added as a lubricant and Guidant respectively. The granules are directly compressed (8 mm diameter, circular flat faced punches) on a rotary tablet punching machine. Each tablet contained 60 mg of curcumin. All the tablets will store in airtight containers for further study.

Significance of work:

The main significance of these systems which can remain in Intestinal region for several hours and prolongs the intestinal transit time. Prolonged transit improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to proximal small intestines. This work is to improve the bioavailability of curcumin by gastrointestinal tract and to study in-vitro and in-vivo drug release.

REFERENCES

Flávia Chiva Carvalho1, Marcos Luciano Bruschi2, Raul Cesar Evangelista1, 3, Maria Palmira Daflon Gremião1, 3 Mucoadhesive drug delivery systems Brazilian Journal of Pharmaceutical Sciences vol. 46, n. 1, Jan. /mar., 2010.

Ahuja, A.; khar, R. K.; ali, J. Mucoadhesive drug delivery systems. *Drug Dev. Ind. Pharm.*, v.23, n.5, p.489-515, 1997.

Davis SS, Hardy JG, Taylor MJ, Whalley DR, Wilson CG. Comparative study of gastrointestinal transit of a pellet and tablet formulation. Int J Pharm 1984; 21: 167-77.

Sahilhusen I Jethara, Mukesh R Patel and Alpesh D Patel Sustained Release Drug Delivery Systems: A Patent Overview Aperito Journal of Drug Designing And Pharmacology, 2014.

Rohini D, Alexandar S, Chandrasekar MJN. Preparation and in vitro evaluation of sustained release tablet formulations of metformin HCl. Asian J Pharm Clin Res 2012; 5(1): 45-8.

De R, Kundu P, Swarnakar S, et al. Antimicrobial activity of curcumin against *Helicobacter pylori* isolates from India and during infections in mice. Antimicrob Agents Chemother 2009; 53:1592-1597.

Wang Y J, Pan M H, Cheng A L, et al. Stability of curcumin in buffer solutions and characterization of its degradation products. J Pharma Biomed Anal 1997; 15(12):1867-1876.

Rakesh Das effective mucoadhesive buccal patches: wound healing activity of curcumin & centella asiatica extract compared to rhegf, International Journal of Pharmacy and Pharmaceutical Sciences, 2011.

Rambir Singh, Ramesh Chandra,Mridula Bose , Pratibha Mehta Luthra.. Antibacterial activity of Curcuma longa rhizome extract on pathogenic bacteria. Current Science, Vol. 83, issue 6, 25 Sept. 2002, page 737-740.

D. Gopinath, M. Rafiuddin Ahmed, K. Gomathi, K. Chitra, P. K.Sehgal, R. Jayakumar.Dermal wound healing processes withcurcumin incorporated collagen films. Biomaterials, Volume 25,Issue 10, May 2004, Pages 1911-1917.

Mishra S, Kumar G, Kothiyal P (2012) Formulation and Evaluation of Buccal Patches of Simvastatin by Using Different Polymers. The Pharma Innovation 1: 87-92.

Shaikh R, Raghurai ST, James GM, David WA, Donnelly R (2011), Mucoadhesive drug delivery systems. J of Pharm and Bioallied Sci 3: 89-100.

Kumar K, Dhawan N et al. (2014) Bioadhesive polymers: Novel tool for drug delivery. Artificial Cells. Nanomed. Biotech 42: 274-283.

Lalla JK, Gurnancy RA (2002) Polymers for mucosal Delivery-Swelling and Mucoadhesive Evaluation. Indian Drugs.

Alexander A, Ajazuddin S, Tripathi DK, Verma T, Swarna G, et al. (2011) Mechanism responsible for mucoadhesion of mucoadhesive drug delivery system: a review. Int J App Bio and Pharm Tech 2: 434-450.

Ramana MV, Nagdaand C, Himaja M (2007) Design and Evaluation of Mucoadhesive Buccal Drug Delivery Systems containing Metoprolol Tartrate. Ind J of P'ceutical Sci 69: 515-518.

Kolli CS, Gannu R, Yamsani VV, Kishan V, Yamsani MR (2008) Development of Mucoadhesive Patches for Buccal Adminstration of Prochlorperazine: Evaluation of in–vitro Release and Mechanical Properties. Int J of P'eutical Sci and Nanotech 1: 64-70.

Naga Raju K, Velmurugan S, Deepika B, Vinushitha S (2011) Formulation and in-vitro Evaluation of Buccal Tablets of Metoprolol Tartrate. Int J of Pharm and P'ceutical Sci 3: 239–246.

Mishra S, Kumar G, Kothiyal P (2012) Formulation and Evaluation of Buccal Patches of Simvastatin by Using Different Polymers. The Pharma Innovation 1: 87-92.

Sandhya P, Tazyeen N, Sunitha M, Sirisha M, Sunil M (2013) Formulation and Evaluation of Buccal Films of Ketorolac Tromethamine. J of Global Trends in P'ceutical Sci 4: 1184-1192.

Velmurugan S, Srinivas P (2013) Formulation and in- vitro Evaluation of Losartan Potassium Mucoadhesive Buccal Tablets. Asian J Pharm Clin. Res 125-130.

Mehraj Ud Din G, Mohan G, Sharma S, MohiUdDin S, Shukla TP, et al. (2014) Formulation development and Evaluation of Mucoadhesive Buccal Film of Methyldopa. J of Global Trends in P'ceutical Sci 1893–1904.

Madhuri C, Mahendra K (2015) Design of Solid Dosage Form for Buccal Drug Delivery of Diltiazem Hydrochloride. Int J of Pharm. and P'ceutical Res 4: 30-44.

Nagarani K, Krishnaveni J, Kommera H, Sinha LK, Prakash Rao AH (2016) Formulation and Evaluation of Esomeprazole Mucoadhesive Buccal Tablets. Eur J of P'ceutical and Med Res 3: 365-377.

Marimutho J, Varghese N (2016) Formulation and Evaluation of Zidovudine Mucoadhesive Buccal Patches. Int J of P'cology and P'ceutical Sci 3: 30-40.

Bhatt D.A., Pethe A.M. Mucoadhesive drug delivery systems: An Overview. Journal of Pharmacy Research, 2010; 3(8): 1743-1747.

Schnürch A B. Mucoadhesive Systems in Oral Drug Delivery. Drug Discov Today, 2005; 2(1): 83-87. 3.

Khan Ab et al. Review on Mucoadhesive drug delivery system: novel approaches in modern era. Journal of pharmaceutical science, 2014; 4: 128-40. 4.

Rahamatullah Shaikh TR et al. Mucoadhesive drug delivery systems. J Pharm Bioall Sci., 2011; 3: 89-100. 5.

Khurana SH et al. Mucoadhesive drug delivery: mechanism and methods of evaluation. Int J Pharm Biosci, 2011; 2: 458-67.

Jain, S., Dhaliwal, S., Rana, M., Hardevinder, P.S., Tiwary, A.K. Sustained release drug delivery system. US20110244034 (2011).

Davis R.D., Blume R.W., Keyser D.J. Sustained release of guaifenesin combination drugs. US8012504 (2011). Shridhar GS, Manohar SD, Bhanudas RS (2013) Mucoadhesive buccalDrug delivery: An Overview. J of Adv Pharm Edu & Res 3: 319–332.

Chickering DE, III, Mathiowitz E. Fundamentals of bioadhesion. In: Lehr CM, editor. Bioadhesive drug delivery systems-Fundamentals, Novel Approaches and Development. New York: Marcel Dekker; 1999. pp. 1–85

Dodou D, Breedveld P, Wieringa P. Mucoadhesives in the gastrointestinal tract: Revisiting the literature for novel applications. Eur J Pharm Biopharm. 2005;60:1–16

Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Delivery Rev. 2005;57:1556–68

Dodou D, Breedveld P, Wieringa P. Mucoadhesives in the gastrointestinal tract: Revisiting the literature for novel applications. Eur J Pharm Biopharm. 2005;60:1–16

Kinloch AJ. The science of adhesion. J Mater Sci. 1980;15:2141–66.

Jiménez-Castellanos MR, Zia H, Rhodes CT. Mucoadhe-sive drug delivery systems. Drug Dev Ind Pharm. 1993;19:143–94.

Shinde A.J, Gastroretentive Drug Delivery System: An Overview, Pharmainfo.net, 6(1). 2008.

Hwang S.J., Park H, Park K, Gastric Retentive Drug-Delivery Systems, Critical Reviews in Therapeut. Drug Carrier Systems, 15(3), 1998, 243–284.